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EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1617	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,781	URADE ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-7 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/20/08*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

The Examiner for this application at the USPTO has changed. Examiner Jean-Louis can be reached at 571-270-3503.

Response to Amendment

This Office Action is in response to the amendment submitted on 03/10/08. Claims 3-7 and 10 are currently pending in the application. Accordingly, claims 3-7 and 10 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Applicant's argument with respect to the 35 U.S.C. § 112, first paragraph for the term prevention is acknowledged. Given applicant's amendment of the term "prevention" to the term "inhibition" such arguments are now moot. Consequently, the rejection of claims 3-7 under 35 U.S.C. § 112, first paragraph is withdrawn.

Applicant's argument with respect to the scope of enablement rejection of claims 3-7 and 10 under 35 U.S.C. § 112, first paragraph is acknowledged. Applicant argues that the specification shows that three structurally dissimilar antagonists are useful in treating brain injury. Examiner, however, disagrees given that applicant is claiming a

method of treating brain injury using compounds defined by their function rather by their structure. In fact, given the structural divergence of the aforementioned compounds in the antagonist genus, one cannot and would not readily envisaged all prostaglandin receptor antagonists that are useful in the treatment of brain injury rendering this task burdensome. Moreover, because of the variability found in the structures, one of ordinary skill in the art would not predictably concur that all prostaglandin D receptor antagonist can treat brain injury. As a result, the scope of enablement rejection of claims 3-7 and 10 under 35 U.S.C. § 112, first paragraph is maintained.

Applicant's argument with respect to Tsuri or Wong as not teaching or suggesting applicant's invention has been fully considered but is not persuasive. Examiner would like to further point out that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The rejections of claims 3-7 and 10 were made over Tsuri in view of Wong which rendered applicant's invention obvious. Tsuri et al. teaches (ZS)-7-[(1R,2R,3S,5S)-2-(5-hydroxybenzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3yl]hept-5-enoic acid via modification of compound 14 using R-group 19 and compound (ZS)-7-[(1R,2R,3S,5S)-2-(5-benzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3yl]hept-5-enoic acid via modification of compound 14 using R-group 18 as potent selective antagonists of prostaglandin D2 receptors. Tsuri et al. further teaches that these compounds are effective in reducing intranasal pressure largely due to their inhibition of

vascular permeability (i.e. edema), reduction of smooth muscle cell (found in vascular cells) contractility as well as reducing the number of immune cells (i.e. eosinophils) infiltrates. Consequently, these data suggest that the aforementioned PGD2 receptor antagonists are helpful in reducing inflammation, edema, and vascular permeability. In the specification, applicant defined treatment of brain injury encompasses brain edema, cerebral bleeding (as a result of vascular permeability), and cerebrovascular disorders. Wong et al., on the other hand, teaches the pathophysiology associated with primary brain injury. Following brain injury, a primary inflammatory response is triggered which increases vascular permeability (i.e. Cerebral bleeding) and vasodilation that leads to vasogenic edema, cerebral ischemia and impaired autoregulation which consequently results in cytotoxic edema that exacerbates the existing cerebral ischemia resulting in secondary brain injury. Thus, in view of applicant's definition of the treatment of brain injury, one of ordinary skill in the art would have found it obvious to utilize the compounds of Tsuri et al. given their efficacy in inhibiting increases in microvascular permeability and their efficacy in reducing inflammation due to their effects on eosinophils. Moreover, one of ordinary skill in the art would have found it obvious to utilize the aforementioned compounds in the treatment of brain injury as brain injury is characterized by inflammation, edema formation and vascular permeability. As a result of the combined teachings of Tsuri in view of Wong, claims 3-7 and 10 are rendered obvious and the rejection is therefore maintained.

For the foregoing reasons, the rejection of claims 3 - 7 and 10 under 35 U.S.C. § 112, first paragraph and 103 (a) remain proper and are maintained. However, in view of applicant's amendment, the following modified 35 U.S.C. § 112, first paragraph and 103 (a) Final rejections are being made.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating brain injury administering some species of prostaglandin D receptor antagonists, does not reasonably provide enablement for the entire genus of prostaglandin D receptor antagonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to a method for treatment or inhibition of brain injury administering an effective amount of prostaglandin D receptor antagonists to a patient in need thereof. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention for treatment or inhibition of brain injury using all prostaglandin D receptor antagonists. Attention is directed to In re Wands, 8

USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdAPIs 1986) at 547 the court recited eight factors:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Nature of the invention:

The instant invention pertains to methods for treating and inhibition brain injury by administering an effective amount of a prostaglandin D receptor antagonist. The invention requires that one of skill be able to make every prostaglandin D receptor antagonist within the genus of such antagonists without empirical, undue and unpredictable trial and error experimentation; i.e., the skilled artisan must be able to readily recognize what structural features confer the antagonist properties of the prostaglandin D receptors and create another antagonist with the same desired characteristic. However, given that applicant defines the antagonists by function rather than by structure, one of ordinary skill would not readily envisaged a prostaglandin

receptor antagonist without undue experimentation. Moreover, the ability to "identify" an antagonist with the desired property to inhibit prostaglandin D receptors is not equivalent to the ability to make and use a prostaglandin D receptor antagonist based on the above principle.

Scope of the invention:

The scope of the invention is very broad, encompassing all antagonists from the genus corresponding to the prostaglandin D2 receptors, which includes both DP-type and CRTH2-type receptors. However, there is only description of a few specific antagonists provided, and there is no description of CRTH2-type receptor antagonists. As such the skilled artisan cannot make the broad scope of the claimed Prostaglandin D2 receptor antagonists.

State of the prior art:

The state of the art with regard to prostaglandin D receptor antagonists administered as treatment for brain injury is poorly developed. No prior art exists specifically describing administration of such antagonists as a therapeutic modality for brain injury in humans.

Relative skill of those in the art:

The relative skill of those in the art is high, typically requiring an advanced professional degree.

Predictability or lack thereof in the art:

The skilled artisan would view that the method for treatment or inhibition of brain injury by administering prostaglandin D (PD) receptor antagonists as being unpredictable due to lack of prior art and the divergent structures of compounds capable of inhibiting the prostaglandin D2 receptors. The state of the prior art itself in regard to the localization or distribution of prostaglandin D receptors in human tissues is a topic of much debate. Initial findings suggested PGD receptor localization limited to the retina and the small intestine; yet, other studies suggested PGD receptor expression on vascular smooth muscle cells as well as localization on T-helper 2 cells. At the time of applicant's invention, the field of prostaglandin D receptor localization and pharmacological development of these receptors was in its infancy of development. As such, the teachings required by applicant to make and use the entire genus of prostaglandin D receptor antagonists is great, because of the variability found in the prior art with regard to receptor affinities and ligand binding specificities of and antagonists for the prostaglandin D receptors DDP-type and CRTH2-type of receptors as well the variability of compounds with divergent structures rendering the expectation of success to be low. Applicants do teach antagonists of DP receptors, yet fail to describe whether these antagonists also have equivalent effects on the CRTH2 receptors and how these receptors are involved in reducing the effects of brain injury. Moreover, the fact that the aforementioned compounds are structurally different suggests that undue burden is needed to delineate every single compound that is a PD

receptor antagonist. Thus without specific teachings by applicant that provide the necessary examples and show the reproducibility of such findings with CRTH2 receptors and PGD antagonists, it must be considered unpredictable as to which PGD receptors are responsible for the effects that applicants regard as their invention or in effect which compounds are actually receptor antagonists.

Amount of guidance provided by the inventor and existence of working examples: In the instant case, 9 working examples are provided in the specification and 27 Figures are included of which 6 (Figures 16, 20 and 24-27) are directly applicable to the PGD2 antagonist. Review of the examples and data provided corresponding to the claimed method of administering a prostaglandin D2 receptor antagonist for treatment of brain injury include the DP-receptor antagonists BW-A868C, pinagladin, and ramatroban; however, these examples do not specifically include any indication as to the effects that would be attributable to the CRTH2 receptors and thus to the genus of prostaglandin D receptor antagonists.

Although Applicant convincingly demonstrates that brain injury results in increased plasma exudate in the brain parenchyma via a time-dependent manner and results in increased infiltration of inflammatory cells, Applicant fails to demonstrate that DP-receptors are critical for either of these responses to brain injury. For example, Applicant shows that mice-deficient in DP receptors by genetic knockout have reduced plasma exudate than wild-type controls, but still, a significant amount of dye leakage is

measured (see Figure 26). Furthermore, pretreatment of mice with DP receptor antagonists BW-A868C or ramatroban or pinagladin fail to completely, or totally eliminate all dye leakage (see Figures 24 and 27) or eliminate inflammatory cell infiltration into the injury site as shown in Figures 16 or 25. Together these data suggest a role for the DP receptor in some aspects of plasma exudation in sites of brain injury and inflammatory cell infiltration, but do not convincingly demonstrate that all types of prostaglandin D receptors and hence, all prostaglandin D receptor antagonists could treat brain injury. Thus, none of the working examples provided teaches a skilled artisan how to treat brain injury via blockade of CRTH2 receptors. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP §2164.

Genetech, 108 F.3d at 1366, states "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague limitations of general ideas that may or may not be workable.

Therefore, in view of the Wands factors, e.g., the lack of direction or guidance provided, absence of working examples, and the lack of predictability of the art as discussed above, to practice the claimed invention herein, an artisan would have to engage in undue experimentation to test whether administration of each and every species of the entire genus of prostaglandin D receptor antagonists could in fact be administered and

treat brain injury with no reasonable expectation of success. To do so, an artisan would have to identify every possible marker of brain inflammation, type of injury method, as well as, conduct pharmacological testing to determine whether prophylactic or acute administration of each and every PGD antagonist could in fact treat patients suffering from brain injury by analyzing each of the markers identified. Finally, an artisan would be required to assess any and all mechanisms by which brain injury may occur and verify that the claimed invention does, in fact provide treatment for brain injury, including evidence of an inflammatory response to tissue injury following a traumatic insult, and have to do so with no assurance of success.

Claim Objections

Claims 4-7 are objected to under 37 CFR 1.75 (c), as being of improper dependent forms for depending on rejected claims. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In particular, claims 4-7 are dependent on claim 3 which stands rejected under 35 U.S.C. § 112, first paragraph (i.e. enablement). Correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-7 and 10 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Tsuri et al. (J. Med. Chem. 1997, Vol. 40, pgs. 3504-3507, previously cited) in view of Wong (Critical Care Nurse, 2000, Vol. 20. No. 5, pgs. 18-27, previously cited).

Tsuri et al. teach the (ZS)-7-[1R,2R,3S,5S)-2-(5-hydroxybenzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid via modification of compound 14 using R-group 19 (see p. 3505); also taught is (ZS)-7-[1R,2R,3s,5s)-2-(5-benzo[b]tiophen-3-ylcarbonylamino)-10-norpinan-3-yl]hept-5-enoic acid via modification of compound 14 using R-group 18 (see p. 3505). Testing of these compounds using an in vivo rhinitis model showed 78% inhibition of intranasal pressure induced by antigen challenge in guinea pigs (see p. 3505, Table 2, compounds 16, 19 and 20). Administration of DP antagonists reduced intranasal pressure largely by inhibiting vascular permeability (edema) and prevention of airway resistance (see p. 3506, Table 3) as well as reduced the number of immune cell (eosinophil) infiltrates (p. 3506, co1.1, lines 35-44). Thus, these data suggest that PGD2 antagonists have promise for alleviating allergic diseases by reducing inflammation. edema, eosinophil infiltration and

bronchial smooth muscle relaxation.

Tsuri et al. does not teach use of PGD2 antagonists as a method for treatment or inhibition of brain injury.

Wong teaches the pathophysiology associated with primary brain injury. Following brain injury, a primary inflammatory response is triggered which increases vascular permeability and vasodilation that leads to vasogenic edema, cerebral ischemia and impaired autoregulation which leads into a cyclical pattern of reduced ATP and increased lactic acidosis, increased ion and water influx into cells, resulting in cytotoxic edema that exacerbates the existing cerebral ischemia resulting in secondary brain injury (see p. 18, col. 3; p. 19, col. 1-2; and p.20, Figure 1).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ PGD2 receptor antagonists of Tsuri et al. for treatment and inhibition of brain injury because of the anti-inflammatory properties of these drugs disclosed in the prior art. Moreover, in view of applicant's definition of the treatment of brain injury that is analogous to treatment of brain edema and cerebral bleeding, one of ordinary skill in the art would have found it obvious to utilize the compounds of Tsuri et al. given their efficacy in inhibiting increases in microvascular permeability (i.e. cerebral bleeding) and their efficacy in reducing inflammation due to their reductive effects on eosinophils. Moreover, one of ordinary skill in the art would have found it obvious to utilize the aforementioned compounds in the treatment of brain injury as brain injury is characterized by inflammation, edema formation and vascular permeability. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the

invention was made to employ the Prostaglandin D receptor antagonists taught by Tsuri et al. in a method to treat a head injury in a patient in order to reduce the possibility of inflammation-induced secondary brain damage resulting from vasogenic and cerebral cytotoxic edema as taught by Wong with the end result being that of applicant's claimed invention (claims 3-6 and 10).

Finally, compounds 18-22 (Scheme 3, see p. 3505) taught by Tsuri et al. teach similar compounds to the prostaglandin D receptor antagonist structure I-Aa as in the instant claim 7 except for the stereochemistry. The difference in stereochemistry is an obvious variation as Tsuri et al. teaches similar stereochemical substitutions for the other compounds found in Schemes 1 and 2, and thus it would have been obvious to make similar substitutions in the compounds made using Scheme 3. In lieu of a showing of unexpected results, one of ordinary skill in the art at the time of the invention would have had a reasonable chance of success to make and use this chemical structure using routine substitutions as are taught by Tsuri et al.

Conclusion

No Claims allowed.

Applicant's amendment necessitated the modified rejections presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

/S. J. L. /

Examiner, Art Unit 1617

07/11/08

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617